PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION RELATING TO PRIORITY CLAIM

(PCT Rules 26bis.1 and 26bis.2 and Administrative Instructions, Sections 402 and 409)

To:

QUAGHEBEUR, Luc
Janssen Pharmaceutica N.V.
Patent Dept. - 3547
Turnhoutseweg 30
B-2340 Beerse
BELGIQUE

Date of mailing (day/month/year) 11 December 2000 (11.12.00)	
Applicant's or agent's file reference JAB 1499-PCT	**IMPORTANT NOTIFICATION**
International application No. PCT/EP00/05675	International filing date (day/month/year) 20 June 2000 (20.06.00)
Applicant JANSSEN PHARMACEUTICA N.V. et al	

The applicant is hereby **notified** of the following in respect of the priority claim(s) made in the international application.

1. [X] **Correction of priority claim.** In accordance with the applicant's notice received on: 30 October 2000 (30.10.00), the following priority claim has been corrected to read as follows:

EP 28 June 1999 (28.06.99) 99202088.3

- [ ] even though the indication of the number of the earlier application is missing.
- [ ] even though the following indication in the priority claim is not the same as the corresponding indication appearing in the priority document:

2. [ ] **Addition of priority claim.** In accordance with the applicant's notice received on: , the following priority claim has been added:

- [ ] even though the indication of the number of the earlier application is missing.
- [ ] even though the following indication in the priority claim is not the same as the corresponding indication appearing in the priority document:

3. [ ] As a **result of the correction and/or addition** of (a) priority claim(s) under items 1 and/or 2, the (earliest) priority date is:

4. [ ] **Priority claim considered not to have been made.**

- [ ] The applicant failed to respond to the Invitation under Rule 26bis.2(a) (Form PCT/IB/316) within the prescribed time limit.
- [ ] The applicant's notice was received after the expiration of the prescribed time limit under Rule 26bis.1(a).
- [ ] The applicant's notice failed to correct the priority claim so as to comply with the requirements of Rule 4.10.

The applicant may, before the technical preparations for international publication have been completed and subject to the payment of a fee, request the International Bureau to publish, together with the international application, information concerning the priority claim. See Rule 26bis.2(c) and the PCT Applicant's Guide, Volume I, Annex B2(IB).

5. [ ] In case where **multiple priorities** have been claimed, the above item(s) relate to the following priority claim(s):

6. A copy of this notification has been sent to the receiving Office and

- [X] to the International Searching Authority (where the international search report has not yet been issued).
- [X] the designated Offices (which have already been notified of the receipt of the record copy).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

Céline Faust

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 05 February 2001 (05.02.01)	
International application No. PCT/EP00/05675	**Applicant's or agent's file reference** JAB 1499-PCT
International filing date (day/month/year) 20 June 2000 (20.06.00)	**Priority date** (day/month/year) 28 June 1999 (28.06.99)
Applicant JANSSENS, Frans, Eduard et al	

1. The designated Office is hereby notified of its election made:

   [X] in the demand filed with the International Preliminary Examining Authority on:

   20 November 2000 (20.11.00)

   [ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

   [ ] was not

   made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Zakaria EL KHODARY
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
JAB 1499-PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/05675	20/06/2000	28/06/1999
Applicant		
JANSSEN PHARMACEUTICA N.V.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 2 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. –

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/05675

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/12 A61K31/437 A61K31/4465 A61K31/4545 A61P11/00
A61P31/12 C07D471/04 C07D401/14 //(C07D471/04,235:00,
221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 92 01697 A (JANSSEN PHARMACEUTICA NV) 6 February 1992 (1992-02-06) page 21, line 9 - line 12	1,10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 December 2000	02/01/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Alfaro Faus, I

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 00/05675

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9201697 A	06-02-1992	AT 188477 T	15-01-2000
		AU 646280 B	17-02-1994
		AU 8209391 A	18-02-1992
		CA 2086546 A	20-01-1992
		CN 1058216 A,B	29-01-1992
		CS 9102239 A	19-02-1992
		DE 69131895 D	10-02-2000
		DE 69131895 T	20-07-2000
		DK 539420 T	29-05-2000
		EP 0539420 A	05-05-1993
		ES 2142802 T	01-05-2000
		FI 930199 A	18-01-1993
		GR 3032999 T	31-07-2000
		HU 64066 A	29-11-1993
		IL 98865 A	27-11-1995
		JP 3085707 B	11-09-2000
		KR 206723 B	01-07-1999
		MX 9100307 A	28-02-1992
		NO 304791 B	15-02-1999
		NZ 238863 A	26-03-1993
		PL 170580 B	31-01-1997
		PT 98366 A,B	29-05-1992
		RU 2067978 C	20-10-1996
		SK 280690 B	12-06-2000
		US 5360807 A	01-11-1994
		ZA 9105654 A	31-03-1993

11 JUL 2001
WIPO PCT

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
JAB 1499-PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/05675	20/06/2000	28/06/1999

International Patent Classification (IPC) or national classification and IPC
C07D401/12

Applicant
JANSSEN PHARMACEUTICA N.V. et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20/11/2000	09.07.2001

Name and mailing address of the international preliminary examining authority:
European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer
Wörth, C
Telephone No. +49 89 2399 8726

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/05675

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-59 as originally filed

Claims, No.:

1-17 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-17
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-17
Industrial applicability (IA)	Yes:	Claims	
	No:	Claims	1-17

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

1. Reference is made to the following documents; they have all been cited in the written opinion:

D1: WO 92 01697 A; 6 February 1992 (1992-02-06)
D2: EP 0099139 A (cited by the Applicant)
D3: EP 0297661 A (cited by the Applicant)
D4: EP 0307014 A (cited by the Applicant)
D5: WO 9810764 A
D6: R.R. TIDWELL ET AL: 'Aromatic Amidines: Comparison of their Ability to Block Respiratory Syncytical Virus Induced Cell Fusion And To Inhibit Plasmin, Urokinase, Thrombin and Trypsin', JOURNAL OF MEDICINAL CHEMISTRY, vol. 26, no. 2, pages 294 to 298
D7: T. CHIBA ET AL: 'Inhibitory Effect of Pyridobenzazoles on Virus Replication in vitro', BIOLOGICAL & PHARMACEUTICAL BULLETIN, vol. 18, no. 8, pages 1081 to 1083
D8: WO 9855120 A
D9: EP 0747363 A
D10 WO 9831363 A

2. Reasoned statement under Art. 35(2) PCT with regard to novelty, inventive st p or industrial applicability; citations and explanations supporting such statement (Reference to section V)

2.1 Novelty

The present application discloses benzimidazoles and imidazopyridines having antiviral activity (see page 1, lines 4-5).

Documents D2 , D3 and D4 disclose bicyclic heterocycles as pharmaceuticals. It appears that the subject-matter of the present application overlaps with documents D2, D3 and D4 with respect to the definitions given for the substituent R^1 in the cited documents. Document D2 (page 2, line 17-19), document D3 (see page 2, line 43) and document D4 (see page 2, line 40) define R^1 inter alia as "lower alkyl substituted with two Ar^1 radicals", which appears to overlap with the definition of the substituent -G-R^1 of the present application with respect to the definition of radical Q as (b-5) or (b-6) given in claim 1 and 3 of the present application, respectively.

As a consequence thereof, the present application appears not to me t th requirements set forth in Article 33(2) PCT.

The present application is considered to be novel over documents D1 and D5-D10 for the following reasons:

D1: substituent "D" (see page 34, line 29) is a unsubstituted alkyl-chain in contrast to substituent "G" (see page 61, lines 9-11) of the present application

D5: no fused heterocycle as core-molecule

D6: radical Q of the present application is the novelty rendering feature

D7: discloses tricyclic compounds

D8: substituent -NH-R^1 of D8 differs from radical Q of the present application

D9: substituent R^2 of D9 differs from radical Q of the present application

D10: substituent -SO_2-R differs from G-R^1 of the present application.

2.2 Inventive step

Documents D8-D10 are considered as respective closest prior art for some of the claimed families of compounds. These documents disclose N1-C2- substituted benzimidazoles and its bioisosteric analogue pyridoimidazole as anti-viral agents (**see D8**, abstracts; page 2, last paragraph: substituted benzimidazoles, which inhibit the growth of picornaviruses; **see D9**, page 2, lines 24ff; **see D10,** abstract and page 2, lines 14-22, substituted pyridoimidazoles, which are at present regarded as bioisosteric analogues to benzimidazoles, useful as antiviral agents).

In view of these documents, the problem to be solved can be regarded as the provision of further fused 5,6-membered heterocyclic compounds with unexpected effects.

It is stated that in contrast to the description, which alleges anti-viral activity for the subject-matter of the present application, the claimed activity (see claim 9-11 and 17) is considered to be "therapeutical effective".

The solution to this problem provided by the present application consists in analogisations of the N1- and C2-substituents of known fused heterocyclic core-molecules or their bioisosteric analogues (see documents D8-D10).

However, the combined technical teaching of documents D2-D4 clearly indicates a fused heterocycle, substituted at least at positions N1 and C2 of the imidazole-moiety, as therapeutically active lead compounds. As a consequence thereof, the man skilled in the art having knowledge of this technical teaching would not be surprised to obtain therapeutically active compounds by broadening the group of possible substituents represented by radical Q or G-R^1 according to the present application.
Moreover, underlying the principles of structure-activity relationship (SAR), it is stressed that for structural similar compounds a similar biological activity can be expected. As a consequence thereof, SAR allow to predict that for formal analogisations the pharmaceutical activity will be maintained.

Therefore, the feature of the enlarged group of possible substituents represented by radical Q or G-R^1 starting from documents D8-D10 is merely one of several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without any exercise of inventive skill, in order to solve the problem defined above.

As far as the alleged anti-viral activity mentioned in the description of the present application is concerned, attention is drawn to documents D6-D7.
For the man skilled in the art, having knowledge of the combined technical teaching of

- document D6 (amidino-benzimidazoles and amidino-indole derivatives as agents exhibiting a high potency against virus-induced cell fusion and anti- viral lead compounds, see page 295, first column, last paragraph),
- document D7 (fused benzimidazoles as compounds exhibiting an inhibitory effect on RSV virus replication; see compounds 1-4, table 1, page 1082),

the analogisation of substituents of benzimidazole or its bioisosteric analogues is also considered as one of several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed.
Furthermore, the inhibitory effect of the known histamine H1 receptor antagonist **cetirizine** on viral replication together with an inhibiting effect of RSV-induced cell modifications disclosed in document D5, page 2, lines 17-22 and page 3, lines 10-13, is a strong hint for a man skilled in the art having knowledge of the technical teaching

of documents D6 and D7 (benzimidazole as lead compound for anti-viral agents) to examine, if known anti-allergic compounds bearing a benzimidazole-core also exhibit anti-viral properties, thereby arriving to the solution proposed by the present application.

It is noted, that SAR does not allow to predict whether the activity is better or worse. As a consequence thereof, an unexpected beneficial effect can be considered as an indication for inventive step. However, the applicant has not yet shown that the claimed compounds are likely to have any unexpected beneficial effects compared to those in the cited documents, in particular the nearest possible compounds, apparently represented by the compounds disclosed in documents D-D10.

As far as the scope of the claims is concerned, attention is drawn to the point, that only such compounds can be claimed which represent a solution of the problem underlying the application in suit. The extent of a reasonable generalisation depends on the credibility that substantially all the alternatives claimed must be a solution to the problem. Extremely broad generalisations like e.g. the definition of radical G are in contradiction to the basis of even qualitative structure-activity- relationships. Taking into account the relevant state of the art and the common knowledge, it appears to be not predictable, that all alternatives would achieve the alleged technical effect.

Accordingly, the present application appears not to fulfill the requirements s t forth in Article 33(3) PCT.

3. Certain observations in the international application (Reference to section VIII)

3.1 The terms "prodrug" and "metal complex" in claim 1 and 8 do not fulfill the requirements of Article 6 PCT. The mere term "prodrug" is a functional expression attempting to define the subject-matter in terms of a desired property instead of indicating precisely the technical measures specifically designed to solve the problem. Functional terms will only be allowable if the solution is one which can directly be verified by tests or procedures adequately specified of known to the person skilled in the art and which verification does not need undue experimentation (cf. Guidelines C-III, 4.7). This requirement is presently not fulfilled.

3.2 Contrary to the requirements of Rule 5.1(a)(ii) PCT, documents D 5-10 are not identified and the relevant background art disclosed therein is not mentioned.

3.3 Attention is drawn to the fact that dependent claims are only admissible in the case of a allowable independent claim (cf. Rule 6.4 PCT).

PATENT COOPERATION TREATY

RECEIVED

11 JUL 2001

Patent department

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

QUAGHEBEUR, Luc
JANSSEN PHARMACEUTICA N.V.
Patent Department - EXT. 3547
Turnhoutseweg 30
B-2340 Beerse
BELGIQUE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	09.07.2001
Applicant's or agent's file reference: JAB 1499-PCT	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/05675	20/06/2000	28/06/1999

Applicant: JANSSEN PHARMACEUTICA N.V. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	THORNTON, J Tel.+49 89 2399-8072

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
JAB 1499-PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/05675	20/06/2000	28/06/1999

International Patent Classification (IPC) or national classification and IPC
C07D401/12

Applicant
JANSSEN PHARMACEUTICA N.V. et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20/11/2000	09.07.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Wörth, C Telephone No. +49 89 2399 8726

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/05675

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-59 as originally filed

Claims, No.:

1-17 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-17
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-17
Industrial applicability (IA)	Yes:	Claims	
	No:	Claims	1-17

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

1. **Reference is made to the following documents; they have all been cited in th written opinion:**

D1: WO 92 01697 A; 6 February 1992 (1992-02-06)
D2: EP 0099139 A (cited by the Applicant)
D3: EP 0297661 A (cited by the Applicant)
D4: EP 0307014 A (cited by the Applicant)
D5: WO 9810764 A
D6: R.R. TIDWELL ET AL: 'Aromatic Amidines: Comparison of their Ability to Block Respiratory Syncytical Virus Induced Cell Fusion And To Inhibit Plasmin, Urokinase, Thrombin and Trypsin', JOURNAL OF MEDICINAL CHEMISTRY, vol. 26, no. 2, pages 294 to 298
D7: T. CHIBA ET AL: 'Inhibitory Effect of Pyridobenzazoles on Virus Replication in vitro', BIOLOGICAL & PHARMACEUTICAL BULLETIN, vol. 18, no. 8, pages 1081 to 1083
D8: WO 9855120 A
D9: EP 0747363 A
D10 WO 9831363 A

2. **Reasoned statement under Art. 35(2) PCT with regard to novelty, inventive st p or industrial applicability; citations and explanations supporting such statement (Reference to section V)**

2.1 Novelty

The present application discloses benzimidazoles and imidazopyridines having antiviral activity (see page 1, lines 4-5).

Documents D2 , D3 and D4 disclose bicyclic heterocycles as pharmaceuticals. It appears that the subject-matter of the present application overlaps with documents D2, D3 and D4 with respect to the definitions given for the substituent R^1 in the cited documents. Document D2 (page 2, line 17-19), document D3 (see page 2, line 43) and document D4 (see page 2, line 40) define R^1 inter alia as "lower alkyl substituted with two Ar^1 radicals", which appears to overlap with the definition of the substituent -G-R^1 of the present application with respect to the definition of radical Q as (b-5) or (b-6) given in claim 1 and 3 of the present application, respectively.

As a consequence thereof, the present application appears not to meet th requirements set forth in Article 33(2) PCT.

The present application is considered to be novel over documents D1 and D5-D10 for the following reasons:

D1: substituent "D" (see page 34, line 29) is a unsubstituted alkyl-chain in contrast to substituent "G" (see page 61, lines 9-11) of the present application

D5: no fused heterocycle as core-molecule

D6: radical Q of the present application is the novelty rendering feature

D7: discloses tricyclic compounds

D8: substituent -NH-R^1 of D8 differs from radical Q of the present application

D9: substituent R^2 of D9 differs from radical Q of the present application

D10: substituent -SO_2-R differs from G-R^1 of the present application.

2.2 Inventive step

Documents D8-D10 are considered as respective closest prior art for some of the claimed families of compounds. These documents disclose N1-C2- substituted benzimidazoles and its bioisosteric analogue pyridoimidazole as anti-viral agents (**see D8**, abstracts; page 2, last paragraph: substituted benzimidazoles, which inhibit the growth of picornaviruses; **see D9**, page 2, lines 24ff; **see D10,** abstract and page 2, lines 14-22, substituted pyridoimidazoles, which are at present regarded as bioisosteric analogues to benzimidazoles, useful as antiviral agents).

In view of these documents, the problem to be solved can be regarded as the provision of further fused 5,6-membered heterocyclic compounds with unexpected effects.

It is stated that in contrast to the description, which alleges anti-viral activity for the subject-matter of the present application, the claimed activity (see claim 9-11 and 17) is considered to be "therapeutical effective".

The solution to this problem provided by the present application consists in analogisations of the N1- and C2-substituents of known fused heterocyclic core-molecules or their bioisosteric analogues (see documents D8-D10).

However, the combined technical teaching of documents D2-D4 clearly indicates a fused heterocycle, substituted at least at positions N1 and C2 of the imidazole-moiety, as therapeutically active lead compounds. As a consequence thereof, the man skilled in the art having knowledge of this technical teaching would not be surprised to obtain therapeutically active compounds by broadening the group of possible substituents represented by radical Q or G-R^1 according to the present application.
Moreover, underlying the principles of structure-activity relationship (SAR), it is stressed that for structural similar compounds a similar biological activity can be expected. As a consequence thereof, SAR allow to predict that for formal analogisations the pharmaceutical activity will be maintained.

Therefore, the feature of the enlarged group of possible substituents represented by radical Q or G-R^1 starting from documents D8-D10 is merely one of several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without any exercise of inventive skill, in order to solve the problem defined above.

As far as the alleged anti-viral activity mentioned in the description of the present application is concerned, attention is drawn to documents D6-D7.
For the man skilled in the art, having knowledge of the combined technical teaching of

- document D6 (amidino-benzimidazoles and amidino-indole derivatives as agents exhibiting a high potency against virus-induced cell fusion and anti- viral lead compounds, see page 295, first column, last paragraph),
- document D7 (fused benzimidazoles as compounds exhibiting an inhibitory effect on RSV virus replication; see compounds 1-4, table 1, page 1082),

the analogisation of substituents of benzimidazole or its bioisosteric analogues is also considered as one of several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed.
Furthermore, the inhibitory effect of the known histamine H1 receptor antagonist **c tirizin** on viral replication together with an inhibiting effect of RSV-induced cell modifications disclosed in document D5, page 2, lines 17-22 and page 3, lines 10-13, is a strong hint for a man skilled in the art having knowledge of the technical teaching

of documents D6 and D7 (benzimidazole as lead compound for anti-viral agents) to examine, if known anti-allergic compounds bearing a benzimidazole-core also exhibit anti-viral properties, thereby arriving to the solution proposed by the present application.

It is noted, that SAR does not allow to predict whether the activity is better or worse. As a consequence thereof, an unexpected beneficial effect can be considered as an indication for inventive step. However, the applicant has not yet shown that the claimed compounds are likely to have any unexpected beneficial effects compared to those in the cited documents, in particular the nearest possible compounds, apparently represented by the compounds disclosed in documents D-D10.

As far as the scope of the claims is concerned, attention is drawn to the point, that only such compounds can be claimed which represent a solution of the problem underlying the application in suit. The extent of a reasonable generalisation depends on the credibility that substantially all the alternatives claimed must be a solution to the problem. Extremely broad generalisations like e.g. the definition of radical G are in contradiction to the basis of even qualitative structure-activity- relationships. Taking into account the relevant state of the art and the common knowledge, it appears to be not predictable, that all alternatives would achieve the alleged technical effect.

Accordingly, the present application appears not to fulfill the requirements set forth in Article 33(3) PCT.

3. **Certain observations in the international application** (Reference to section VIII)

3.1 The terms "prodrug" and "metal complex" in claim 1 and 8 do not fulfill the requirements of Article 6 PCT. The mere term "prodrug" is a functional expression attempting to define the subject-matter in terms of a desired property instead of indicating precisely the technical measures specifically designed to solve the problem. Functional terms will only be allowable if the solution is one which can directly be verified by tests or procedures adequately specified of known to the person skilled in the art and which verification does not need undue experimentation (cf. Guidelines C-III, 4.7). This requirement is presently not fulfilled.

3.2 Contrary to the requirements of Rule 5.1(a)(ii) PCT, documents D 5-10 are not identified and the relevant background art disclosed therein is not mentioned.

3.3 Attention is drawn to the fact that dependent claims are only admissible in the case of a allowable independent claim (cf. Rule 6.4 PCT).

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(71) Applicant *(for all designated States except US)*: JANSSEN PHARMACEUTICA N.V. [BE/BE]; c/o De Corte, Filip - Ext. 3834, Patent Dept., Turnhoutseweg 30, B-2340 Beerse (BE).

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(74) Agent: QUAGHEBEUR, Luc; Janssen Pharmaceutica N.V., Patent Dept. - 3547, Turnhoutseweg 30, B-2340 Beerse (BE).

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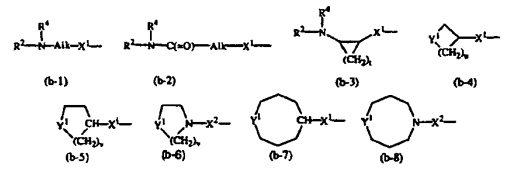
[Continued on next page]

(54) Title: RESPIRATORY SYNCYTIAL VIRUS REPLICATION INHIBITORS


(I)


(b-1) (b-2) (b-3) (b-4) (b-5) (b-6) (b-7) (b-8)

(57) Abstract: This invention concerns the compounds of formula (I), prodrugs, <I>N</I>-oxides, addition salts, quaternary amines, metal complexes or stereochemically isomeric forms thereof wherein -a^1=a^2-a^3=a^4- is a radical of formula -CH=CH-CH=CH-, -N=CH-CH=CH-, -CH=N-CH=CH-, -CH=CH-N=CH-, -CH=CH-CH=N- wherein each hydrogen atom may optionally be substituted; Q is a radical of formula (b-1), (b-2), (b-3), (b-4), (b-5), (b-6), (b-7), (b-8), wherein Alk is C_{1-6}alkanediyl; Y^1 is a bivalent radical of formula-NR^2- or -$CH(NR^2R^4)$-; X^1 is NR^4, S, S(=O), $S(=O)_2$, O, CH_2, C(=O), $CH(=CH_2)$, CH(OH), $CH(CH_3)$, $CH(OCH_3)$, $CH(SCH_3)$, $CH(NR^{5a}R^{5b})$, CH_2-NR^4 or NR^4-CH_2; X^2 is a direct bond, CH_2, C(=O), NR^4, C_{1-4}alkyl-NR^4, NR^4-C_{1-4}alkyl; t is 2 to 5; u is 1 to 5; v is 2 or 3; and whereby each hydrogen in Alk and in (b-3), (b-4), (b-5), (b-6), (b-7) and (b-8), may optionally be replaced by R^3; provided that when R^3 is hydroxy or C_{1-6}alkyloxy, then R^3 can not replace a hydrogen atom in the α position relative to a nitrogen atom; G is substituted C_{1-10}alkanediyl wherein the substituent is attached via an oxygen atom; R^1 is an optionally substituted monocyclic heterocycle or aryl; R^2 is hydrogen, formyl, C_{1-6}alkylcarbonyl, Hetcarbonyl, pyrrolidinyl, piperidinyl, homopiperidinyl, C_{3-7}cycloalkyl or C_{1-10}alkyl substituted with $N(R^6)_2$ and optionally with another substituent; R^3 is hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, arylC_{1-6}alkyl or arylC_{1-6}alkyloxy; R^4 is hydrogen, C_{1-6}alkyl or arylC_{1-6}alkyl; R^{5a}, R^{5b}, R^{5c} and R^{5d} are hydrogen or C_{1-6}alkyl; or R^{5a} and R^{5b}, or R^{5c} and R^{5d} taken together form a bivalent radical of formula -$(CH_2)_s$- wherein s is 4 or 5; R^6 is hydrogen, C_{1-4}alkyl, formyl, hydroxyC_{1-6}alkyl, C_{1-6}alkylcarbonyl or C_{1-6}alkyloxycarbonyl; aryl is optionally substituted phenyl; Het is pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl; as respiratory syncytial virus replication inhibitors; their preparation, compositions containing them and their use as a medicine.

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patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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